Solutions to shortage of liver grafts for transplantation

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Leading article

Solutions to shortage of liver grafts for transplantation

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The success of liver transplantation has resulted in a demand for grafts that exceeds the number of available organs. Organ donation is therefore crucial. This rate of donation depends on numerous factors, including intensive care capacity, funding for organ donation programmes and public awareness. In addition, legislation regarding potential organ donors (opting out or opting in to donation) can influence the number of available organs in a country, although the association between a legislative framework and the level of acceptance rates or absolute number of donors remains unclear[1]. A well organized donation infrastructure along with local commitment for maximizing donation appears to be much more important than any other strategies, but this is a difficult goal to achieve. Other measures have therefore been proposed to increase the pool of available organs. Among those approaches are donation after cardiac death (DCD), the use of fatty or older livers, or the acceptance of donors presenting with a history of cancer. In this issue of *BJS*, three articles attempt to address the impact of donor age on DCD liver grafts[2], the baseline cellular energy status of DCD liver grafts[3] and the risk of cancer transmission in donors with a history of cancer[4].

Donation after circulatory death

Programmes using liver grafts obtained from DCD donors are active in the USA and in six European countries (Spain, UK, Belgium, The Netherlands, Switzerland and Austria). Donors younger than 50 years of age, total donor warm ischaemia time of less than 30 min, and cold ischaemia times below 6 h have been identified as important targets to minimize post-transplant intrahepatic cholangiopathy[5–10]. These widely accepted risk factors are challenged by the study of Detry and colleagues[2]. The authors suggest that donor age *per se* is no longer a contraindication to DCD liver transplantation. They found that graft survival of DCD livers was not affected by higher donor age, up to 3 years after transplantation, when comparing donors older or younger than 70 years. This observation was made, however, in the setting of limited normothermic (less than 20 min) and cold (3·9 h) ischaemic periods. Such attractive ischaemia times could be achieved only by the implementation of a so-called 'comfort therapy' with the use of the volatile anaesthetic agent sevoflurane during the withdrawal phase of life support. Sevoflurane causes rapid anoxia leading, in this series, to a shorter withdrawal phase (median time 11 min). This agent may also confer organ protection through a nitric oxide pathway[11]. In addition, circulatory arrest was defined by an arterial pressure below 40 mmHg, which is an unusual practice in most areas, and the subsequent 'no touch' period was limited to 5 min.

Such an approach would not be possible in many other countries because of strict ethical regulations. For example, in Switzerland the median total warm ischaemia time in donors is 40 min owing to the requirement for certifying brain death after cardiac arrest[12]. As a result, oxygenated cold machine perfusion is used to rescue these marginal grafts[12]. Whether donor age influences outcome in these types of DCD liver, and whether protective strategies are effective regardless of age, has yet to be demonstrated.

Optimizing strategies for liver grafts

Liver grafts exposed to cold or warm ischaemia undergo multiple biochemical and morphological changes, with a switch from aerobic to anaerobic metabolism. DCD organs, in particular, have to tolerate continuous cellular energy consumption during donor downtime, owing to a lack of tissue oxygen. In donors with long intervals of warm ischaemia, new optimizing strategies are therefore needed to avoid irreversible injury to the bile ducts. The article by Perera and co-workers[3] shows key differences in cellular metabolism between human DCD and donation after brainstem death (DBD) liver grafts measured by microdialysis. The authors found cumulated interstitial lactate and glycerol levels in ischaemic livers, consistent with previous data in animal models[13].

Although traditional static cold storage is unlikely to prevent tissue acidosis, machine perfusion appears to be an attractive means of changing biochemical pathways, either before or after procurement, by introducing oxygen to hypoxic tissue. Three

approaches to machine liver perfusion have been reported, differing in perfusate temperature (normothermic, subnormothermic and hypothermic) and the degree of oxygenation. Normothermic machine liver perfusion simulates *in vivo* conditions, and needs dual perfusion through the portal vein and the hepatic artery at physiological flow and temperature with oxygenated diluted blood and nutritional compounds as perfusate. In contrast, both subnormothermic (20–25°C) and hypothermic (2–10°C) machine liver perfusion rely on the dissolved oxygen in a blood-free perfusate. Human data on *ex situ* normothermic or subnormothermic oxygenated liver perfusion and subsequent transplantation are awaited. Preliminary data on discarded human livers suggest the feasibility of both approaches[14,15], and the first clinical results after transplantation of cold perfused DCD[12] and DBD[16] livers suggest benefit.

Expanding the organ donor pool

Transmission of malignant cells by transplantation is a rare, but highly feared, risk in the immunosuppressed patient. Guidelines have been developed to minimize the risk of cancer transmission. The actual risk of cancer transmission by donors against the mortality of patients waiting for a graft in the UK is therefore welcomed[4]. Sixty-one (0·4 per cent) of 17 369 donors were identified retrospectively to carry a high risk of transmission of cancer, according to current guidelines[4]. During 10 years of follow-up, however, no cancer transmission was recorded in any recipient receiving an organ from those donors. Instead, the additional survival benefit of transplanting organs from donors with an unacceptable risk of cancer transmission accumulated to 944 life-years gained. This finding may justify careful expansion of the donor pool by modifying present guidelines. For example, based on this, patients with curative resected melanoma with a tumour thickness of less than 1 mm, or women with curatively resected stage 1 breast cancer, could be considered for organ donation, after a minimum cancer-free period of 5 years. As a means of extending the donor pool for solid organ transplantation, confirmation of these results should result in revised guidelines.

Disclosure

The authors declare no conflict of interest .

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